UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

IN RE NUVARING® PRODUCTS LIABILITY LITIGATION	)	Case No. 4:08-MD-1964 RWS
	)	ALL CASES

MEMORANDUM AND ORDER

Defendants in this matter (hereinafter "Organon") bring a motion to exclude opinions that hormones "counterbalance" and that surrogate markers can assess the risk of VTE in the use of hormonal contraceptives. Organon presents these umbrella motions by attacking the reliability of these opinions generally, rather than by addressing any particular expert's methodology. Organon also argues that these opinions will be unhelpful to the jury. Organon argues that these deficiencies are so egregious that the challenged testimony should be excluded from being tested by any cross-examination at trial, being weighed by any jury, or even limited in any respect by any trial judge. Plaintiffs respond that these opinions are backed by reputable studies and will assist the jury. For the reasons that follow, Organon's motion is denied.

I. BACKGROUND

This multi-district litigation (MDL) relates to the manufacture, marketing, and sale of the prescription pharmaceutical known as NuvaRing. NuvaRing, which is manufactured, marketed, and sold by Organon, is a member of a class of prescription drugs known as combined hormonal contraceptives ("CHCs"). Unlike oral CHCs, NuvaRing takes the form of a flexible ring which releases hormones over the course of treatment. The ring is vaginally inserted by women for birth control. Each month, the ring is removed and a new ring is inserted.

CHCs contain an estrogen, typically ethinyl estradiol ("EE"), and a progestin. The "generation" of CHC depends upon the type of progestin. Each "generation" of CHC typically includes the following progestins: first-generation contains norethynodrel; second-generation contains levonorgestrel; and third-generation CHCs contain desogestrel, gestodene, or norgestimate. NuvaRing uses the active metabolite of desogestrel, etonogestrel, and is therefore considered a third-generation progestin.

First-generation CHCs are characterized by high levels of EE and are associated with high incidence rates of venous thromboembolism ("VTE"), including deep vein thrombosis and pulmonary embolism.[1] Second-generation CHCs use a reduced amount of EE and are associated with lower risk for VTE. It is generally accepted that risk of thrombosis is correlated with estrogen dose.

Third-generation CHCs use lower amounts of estrogen than prior generations. However, some studies have found an increased risk for VTE with some third-generation CHCs as compared to second-generation CHCs. Plaintiffs allege that the third-generation progestin used in NuvaRing, etonogestrel, has been linked to an undisclosed higher risk for VTE, including both deep vein thrombosis and pulmonary embolism. Plaintiffs have asserted the following claims: strict products liability for defective manufacturing, defective design, failure to test, and inadequate warnings; breach of express / implied warranties; and negligence.

In support of their claims, Plaintiffs seek to admit expert testimony that NuvaRing use presents an increased risk for VTE when compared with second-generation use. Plaintiffs' experts intend to testify that this increased risk results from the reduced ability of etonogestrel to

[1] Venous thromboembolism is a blood clot that forms within a vein. Deep vein thrombosis is a blood clot that forms in a vein not externally visible, typically in the veins of the lower extremities. A pulmonary embolism forms when part or all of a blood clot breaks free and lodges in one of the lungs. These conditions have varying severity and can be life threatening.

counterbalance the prothrombotic (blood-clotting) effects of the estrogen component. Plaintiffs' experts also offer opinions that certain biomarkers are associated with an increased risk for VTE and that NuvaRing is associated with an increase in those biomarkers.

Although Organon argues for the exclusion of testimony, Organon does not challenge the qualifications or methods of any individual experts in this motion. Rather, Organon brings an umbrella motion against the reliability of any testimony that 1) etonogestrel fails to counterbalance the prothrombotic effects of EE and 2) biomarkers can assess the risk of VTE.

II. LEGAL STANDARD

Federal Rule of Evidence 702 and Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), govern the admissibility of expert testimony. The Daubert standard applies to all expert testimony, whether based on scientific competence or other specialized or technical expertise. See Polski v. Quigley Corp., 538 F.3d 836, 838 (8th Cir. 2008). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

"When faced with a proffer of expert scientific testimony, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" Polski, 538 F.3d at 838 (quoting Daubert, 509 U.S. at 592–93). Thus, under Rule 702, the trial judge also acts as a gatekeeper by screening evidence for relevance and reliability. Daubert, 509 U.S. at 589. "Rule 702 reflects an attempt to liberalize the rules governing the admission of expert testimony. The rule clearly is one of admissibility rather than

exclusion." Lauzon v. Senco Prods., Inc., 270 F.3d 681, 686 (8th Cir. 2001) (internal quotations and citations omitted). "The exclusion of an expert's opinion is proper only if it is so fundamentally unsupported that it can offer no assistance to the jury." Wood v. Minn. Mining & Mfg. Co., 112 F.3d 306, 309 (8th Cir. 1997) (internal quotations and citation omitted).

When assessing the reliability of expert testimony, a trial court should consider several factors, including: "(1) whether the concept has been tested, (2) whether the concept has been subject to peer review, (3) what the known rate of error is, and (4) whether the concept is generally accepted by the community." Miller v. Baker Implement Co., 439 F.3d 407, 412 (8th Cir. 2006) (citing Daubert, 509 U.S. at 593–95). There is no requirement that courts rely on each factor, as the gatekeeping inquiry is flexible and must be "tied to the facts" of the particular case. Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150 (1999) (quoting Daubert, 509 U.S. at 591).

"[T]he rejection of expert testimony is the exception rather than the rule." Robinson v. GEICO General Ins. Co., 447 F.3d 1096, 1100 (8th Cir. 2006) (citing Fed. R. Evid. 702 advisory comm. note). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 595.

III. ANALYSIS

A. Ability of Surrogate Markers to Assess VTE Risk

Plaintiffs intend to call Dr. Stephen Shohet, an internist and hematologist, Dr. John Richart, a hematologist, and Dr. Scott Roseff, a reproductive endocrinologist, to testify regarding the effect of NuvaRing on blood clotting factors. Plaintiffs' experts will testify that the body creates blood clots by combining a number of blood clotting factors to form a soluble blood

plasma protein. Through further biochemical reactions, this protein is transformed into a long ropelike molecule called Fibrin, which then entraps cellular blood elements to form a clot.

Because the clotting process, if left unchecked, would clot the entire cardiovascular system, the body has a number of counterbalancing control pathways to limit the clotting process. One such system involves Activated Protein C ("APC") which combines with another co-factor, Protein S, to limit the effectiveness of blood clotting factors. Another inhibitory system involves Tissue Factor Pathway Inhibitor ("TFPI") which limits the Tissue Factor blood clotting factor. Protein S, alone, can also inhibit some blood clotting factors. Both Protein S and TFPI are lowered by oral birth control medications. (Doc. 1379, Exh. 16, "Shohet Report," at 9).

Humans can inherit a resistance to the function of APC; this is resistance is known as "APCr." APCr has been shown to increase the risk of VTE. (Shohet Report at 10). Dr. Jan Rosing, a scientist based in the Netherlands, has developed a test for APCr, known as the "Rosing Test" or the "EPT Test," which he used to measure APCr in women taking hormonal contraceptives; this study was published in the *British Journal of Haematology* in 1997. Elevated levels of APCr have been found in subjects using birth-control medicines. (Shohet Report at 10). APCr, as measured by the Rosing Test, has since been validated to predict thrombosis risk in women using hormonal birth control. (Shohet Report at 10 (citing Tans, et al., "Activated Protein C Resistance Determined with a Thrombin Generation-based Test Predicts for Venous Thrombosis in Men and Women," British J. Haematology 2003, 122:465–70); Doc. 1379, Exh. 13, "Richart Report," at pt. V (citing de Visser, et al., "Determinants of the APTT- and ETP-based APC sensitivity Tests," J. Thrombosis & Haemostasis 2005, 3:1488–94)). The Rosing Test has also been used to measure the combined influence of changes in Protein S and TFPI. (Shohet Report at 9–10).

Sex hormone binding globulin ("SHBG") is a protein produced in the liver that increases with estrogen exposure in a dose-dependent manner. (Richart Report at pt. V (citing Van Vliet, et al., Association between sex hormone-binding globulin levels and activated protein C resistance in explaining the risk of thrombosis in users of oral contraceptives containing different progestogens, Human Reproduction 2005, 20:563–568)). SHBG positively correlates with APCr. Id. SHBG also positively correlates with hormone-induced VTE risk. (Doc. 1379, Exh. 22, "Roseff Report," at 16; Richart Report at pt. V).

1. APCr

Organon argues that testimony related to APCr should be barred because it has not been clinically validated as a surrogate marker for VTE risk and because there are no recognized "safe" or "unsafe" levels of APCr. Organon further argues that the Rosing Test is unreliable because it has only been performed in one laboratory and has not been replicated. Finally, Organon argues that APCr has not been generally accepted as a surrogate endpoint for VTE.

Organon's arguments that APCr must be "clinically" validated and that it is unreliable because "safe/unsafe" levels are unknown both lack merit. The record reflects that APCr is not used in a clinical setting and has no clinical utility. (Doc. 1310, Exh. A, Deposition of John Richart, Oct. 21, 2011).[2] As discussed, there is evidence that APCr has been validated outside the clinical setting. Organon's arguments do not reflect methodological deficiencies, but rather, disagreement as to conclusions. Further, although APCr has not been generally accepted as a surrogate endpoint for VTE, general acceptance is only one factor under a Daubert inquiry. See Miller, 439 F.3d at 412.

[2] Strangely, Organon's exhibit containing the deposition of Dr. Richart was missing several pages of testimony. Fortunately, Plaintiffs provided a complete version as one of their exhibits for a related motion.

Both of Plaintiffs' experts cite numerous peer-reviewed studies that validate APCr as measured by the Rosing Test for VTE risk. The record also reflects the use of the Rosing Test in a number of countries outside of the Netherlands. (Doc. 1379, Exh. 18, Deposition of Dr. Shohet, Oct. 6, 2011, at 439). Moreover, these arguments against the reliability of the Rosing Test and APCr's association with VTE risk have been rejected by other courts adjudicating hormonal contraceptive claims. See, e.g., in re Yasmin & YAZ (Drospirenone) Mktg., Sales, Practices & Prods. Liab. Litig., 3:09-MD-02100-DRH, 2011 WL 6302889 (S.D. Ill. Dec. 16, 2011). I find that Plaintiffs' experts may testify about the ability of APCr to predict VTE risk.

2. SHBG

Organon applies its arguments against the admission of APCr testimony to SHBG. As with APCr, SHBG has been subjected to peer-reviewed testing. Although there is no general scientific consensus as to the use of SHBG as a surrogate endpoint for VTE, there are reliable scientific bases for the opinions of Plaintiffs' experts as to SHBG. Organon's objections as to SHBG reflect a dispute as to the conclusions of Plaintiffs' experts, rather than the reliability of the methods underlying those conclusions. I find that Plaintiffs may present testimony as to the link between SHBG and risk for VTE. Organon may present its own evidence to the contrary at trial.

3. "Other hematological findings"

In a footnote, Organon argues against the admission of "other hematological findings [that] may be surrogate markers for VTE." Organon fails to identify which opinion this point addresses, or even which of Plaintiffs' experts might give the opinion. I cannot make a ruling on such a vague assertion.

Insofar as this argument addresses Protein S and Tissue Factor Pathway Inhibitor, I find that there are sufficient indicia of reliability to admit those opinions. Dr. Shohet's report states that both Protein S and TFPI are lowered by oral birth control medications. Studies have shown this effect to be greater in formulations using third-generation progestins than in second-generation progestins. This effect was confirmed when subjects on second-generation progestins were switched to third-generation progestins and *vice versa*. (Shohet Report at 9). These findings have been published in peer-reviewed journals. I find that Plaintiffs have carried their burden of showing the reliability of these opinions.

B. Progestin "Counterbalancing"

Plaintiffs' experts intend to testify that progestin counterbalances the prothrombotic effects of estrogen and that third-generation progestins counterbalance to a lesser degree than second-generation progestins. Organon presents three arguments against the reliability of testimony related to progestin counterbalancing. First, Organon argues that "progestin counterbalancing" has not been adopted by the general scientific community. Second, Organon argues that the theory is not the product of testing or research. Third, Organon argues that there are no data to support progestin counterbalancing. For the reasons that follow, I find that progestin counterbalancing is based on reliable methodology.

Although Organon is correct that "progestin counterbalancing" has not been adopted by the general scientific community, neither has it been rejected by that community. The record reflects that an ongoing debate exists as to the validity of the theory and the data underlying it. Moreover, "general acceptance by the scientific community" is only one factor for reliability under Daubert.

Contrary to Organon's remaining arguments, Plaintiffs' experts cite several studies in support of the theory. See, e.g., (Shohet Report at 8) (citing Kemmeren, et al., Effect of second- and Third-generation oral contraceptives on the protein C system in the absence or presence of the factor V Leiden mutation: a randomized trial. Blood 2004; 103:927–33; Weigratz, I & Kuhl, H, Metabolic and clinical effects of progestogens. Eur. J. Contracept. Reprod. Health Care 2006; 11:153–61). Plaintiffs' experts further support this view by citing to epidemiological studies demonstrating a difference in thrombosis generation amongst androgenic and non-androgenic progestins.[3] Additional support derives from studies evaluating different effects upon Protein S and other blood coagulants and anti-coagulants amongst second- and third-generation progestins.

Plaintiffs have provided sufficient support for the reliability of their experts' theory that progestins counterbalance the blood-clotting effects of estrogens. Though Organon disputes the conclusions of Plaintiffs' experts, Daubert challenges are not intended to adjudicate the merits of conclusions. Organon will have the opportunity to develop the issue more fully during cross-examination and through its own evidence.

C. Assistance to the Finder of Fact

Organon finally argues that neither progestin counterbalance nor surrogate markers will be helpful to the finder of fact. Organon premises this argument upon the absence of data for any individual plaintiff.

Arguments as to the presence or absence of data for a particular plaintiff must be addressed in the context of each individual plaintiff's case. See Kumho Tire Co., 526 U.S. 137 at 150. Moreover, Plaintiffs' claims are grounded, in part, upon allegations of failure to test and inadequate warnings of the increased risk for VTE and other cardiovascular disorders presented

[3] Androgen is a general term for male sex hormones. See (Shohet Report at 11).

by use of NuvaRing. I find that the opinions Organon challenges within this motion will provide assistance to the jury in adjudicating Plaintiffs' claims.

IV. CONCLUSION

For the foregoing reasons, I find the opinions of Plaintiffs' experts challenged here to be grounded in credible articles, studies and reports and, as such based upon reliable methodology. I further find these opinions to be helpful to the finder of fact.

Accordingly,

IT IS HEREBY ORDERED that Defendants' motion to exclude opinions that hormone "counterbalance" or surrogate markers can assess the risk of VTE in the use of hormonal contraceptives [Doc. 1307] is **DENIED.**

RODNEY W. SIPPEL
UNITED STATES DISTRICT JUDGE

Dated this 4th day of March, 2013.